

# EXHIBIT A

## PHS Employee Invention Report

Use plain paper if more space is needed.

For Patent Branch Use

E-Number

E-083-02/0

U.S.P.A.#

U.S. Filing (date)

### Part I: To Be Completed by the Inventor

First Inventor's Name: Teizo Yoshimura

Phone No. (301)846-5518

1. Give a short descriptive title of your discovery or invention.

A novel method to promote maturation of macrophage and dendritic cells

2. Please provide (in non-scientific terms if possible) a one paragraph description of the essence of your discovery or invention and identify the public health need it fills.

After emigration of leukocytes into tissues, they interact with a wide variety of agents, including cytokines and the components of extracellular matrix. Previous studies indicated that collagen could promote maturation of dendritic cells in vitro, however the mechanisms remain unknown. Discoidin domain receptor 1 (DDR1) is a receptor tyrosine kinase activated by the binding to collagen, the major components of the ECM. In this invention, we identified inducible induction of DDR1 in human leukocytes. Our study with DDR1-overexpressing human leukemic cells line, THP-1, suggests that activation of DDR1 with agents such as DDR1-activating anti-DDR1 antibodies, or small molecules could enhance maturation or differentiation of macrophages and dendritic cells. This method would help to produce highly mature dendritic cells with high antigen-presenting activity in vitro. These cells would be used to induce dendritic cell-based immunity to a wide range of antigens, including cancer cells.

3. Who contributed to the invention or discovery? Please identify all colleagues who *could* merit co-authorship credit for the associated publication, whether or not you believe them to be "co-inventors."

Hiddenobu Kamohara  
Wataru Matsuyama

4. Is anyone outside of the Public Health Service aware of your invention or discovery? If so, please identify them and describe the dates and circumstances.

No

5. Are you aware of any PHS patent applications that are related to your invention or discovery?

No

6. Please list the most pertinent previous articles, presentations or other public disclosures, made by you or by other researchers, that are related to your invention or discovery. Also, attach copies, *please!*

Lu et al., J. Exp. Med. 179:1823-1834, 1994  
Mahnke et al., J. Leukoc. Biol. 60:465-472, 1996  
Brand et al., Eur. J. Immunol. 28:1673-1680, 1998.  
Kamohara et al. FASEB J., (October 18) 10.1096/fj.01-0359fje, 2001  
Banchereau et al., Cell, 106:271-274, 2001

7. Please indicate any future dates on which you will publish articles or make *any* presentations related to your invention or discovery.

We plan to show some of results at a meeting on [REDACTED]

8. In one paragraph, please speculate (and be creative!) about possible commercial uses of your invention or discovery.

Currently several cytokines, such as granulocyte-macrophage colony stimulating factor, interleukin-4, or tumor necrosis factor-alpha, or other activators are used to produce dendritic cells in vitro. DDR1 activating agents such as anti-DDR1 activating antibody or small molecular weight agonists, in addition to other agents described above, would be used to promote maturation of dendritic cells in vitro for dendritic cell-based immunotherapy for cancer and other diseases.

9. a. Is the subject matter of your invention related to a PHS CRADA (Cooperative Research and Development Agreement) involving your laboratory or ICD?

☒ No

☐ Yes. If yes, please identify the collaborator: \_\_\_\_\_

- b. Is the subject matter based on research materials that you obtained from some other laboratory?

☒ No

☐ Yes. If yes, please attach any material transfer agreements (MTA) under which you received the material.

10. What companies or academic research groups are conducting similar research (if you know)? Can you identify any companies that may be good licensing prospects?

I do not know.

11. What further research would be necessary for commercialization of your invention? Generally, what are your future research plans for the invention and/or for research in areas related to the invention?

[REDACTED]

12. Human Subject Certification: Does this invention rely upon data involving human subjects as defined in and regulated under 45 CFR Part 46?

☐ No

☒ Yes - If "yes," please provide the Institutional Review Board (IRB) protocol approval number and date: OH99-C-N046, 10/13/99 or explain fully below:

99-CC-0168, 8/24/99

13. First Inventor Information: (Provide this information for each inventor who contributed to the essence of the invention. If more than one, use Page 4, "Information on Additional Inventors.")

Name	Degree	Social Security No. (optional)
Teizo Yoshimura	M.D., Ph.D.	[REDACTED]

Position Title Senior Investigator		Office address Bldg. 559, Rm. 9
Office Phone No. (301)846-5518	FAX No. (301)846-6924	Citizenship <input type="checkbox"/> U.S. <input checked="" type="checkbox"/> Other: Japan
Home address 5709 Etzler Road, Frederick, MD 21702		

Affiliation

☒ ICD (specify ICD and applicable box below)

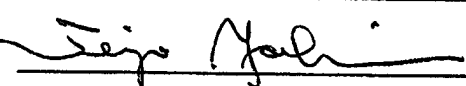

<input type="checkbox"/> GS	<input type="checkbox"/> CO	<input type="checkbox"/> Visiting Scientist	<input type="checkbox"/> Special Volunteer
<input type="checkbox"/> GM	<input type="checkbox"/> Visiting Fellow	<input type="checkbox"/> Howard Hughes Fellow	<input type="checkbox"/> Other (specify):
<input type="checkbox"/> SES	<input type="checkbox"/> Visiting Associate	<input type="checkbox"/> Guest Researcher	

☐ Non-ICD Affiliation (specify):

If more than one inventor, what specific contribution did you make to this work?

#### 14. Inventors' Signatures

- This report is submitted pursuant to Executive Order 10096 and 10930 and/or Department Regulations. PHS employees have an obligation to report inventions they make while employed by PHS to OTT. Under E.O. 10096 and 367 CFR 501 the Government shall obtain the entire right, title, and interest in inventions: (i) made during working hours; or (ii) with Government facilities, equipment, materials, funds or information; or (iii) which bear a direct relationship or is made in consequence of the official duties of the inventor. If you are employed by PHS to conduct or perform research it is presumed that the invention was made under the foregoing circumstances. If this is not the case you must contact your Technology Development Coordinator (TDC) and provide the TDC with the details pertaining to this particular discovery or invention so that a determination of rights can be made.

Inventors' Signatures	Dates	Witnesses' Signatures	Dates
	1/9/02		1/9/02

### Part II: To be completed by the Technology Development Coordinator.

15. Institute(s) or Agency(s) sponsoring this invention

NCI

16. Patent prosecution fees are to be charged to

To be determined

CAN:			
ICD:			
Authorizing Official (Typed)	Signature		Date

► Send 3 copies of this form when completed to the OTT Patent Branch.

### Information on Additional Inventors (copy this page as needed)

Name	Degree	Social Security No. (optional)
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Position Title		Office address
Office Phone No.	FAX No.	Citizenship
Home address		

**Affiliation**

☐ ICD (specify ICD and applicable box below) \_\_\_\_\_

<input type="checkbox"/> GS	<input type="checkbox"/> CO	<input type="checkbox"/> Visiting Scientist	<input type="checkbox"/> Special Volunteer
<input type="checkbox"/> GM	<input type="checkbox"/> Visiting Fellow	<input type="checkbox"/> Howard Hughes Fellow	<input type="checkbox"/> Other (specify): _____
<input type="checkbox"/> SES	<input type="checkbox"/> Visiting Associate	<input type="checkbox"/> Guest Researcher	

☐ Non-ICD Affiliation (specify): \_\_\_\_\_

What specific personal contribution did she/he make to this work?

Name		Degree	Social Security No. (optional)
Position Title		Office address	
Office Phone No.	FAX No.	Citizenship	
Home address			

**Affiliation**

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☐ Non-ICD Affiliation (specify): \_\_\_\_\_

What specific personal contribution did she/he make to this work?

Name		Degree	Social Security No. (optional)
Position Title		Office address	
Office Phone No.	FAX No.	Citizenship	
Home address			

**Affiliation**

☐ ICD (specify ICD and applicable box below) \_\_\_\_\_

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☐ Non-ICD Affiliation (specify): \_\_\_\_\_

What specific personal contribution did she/he make to this work?